UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte GARY D. HODGEN

Appeal No. 2006-0758
Application No. 09/313,628

ON BRIEF

Before SCHEINER, ADAMS and GRIMES, Administrative Patent Judges.

SCHEINER, Administrative Patent Judge.

DECISION ON APPEAL

This appeal involves claims directed to a method of achieving contraception in a human female by administering a combination of a Selective Estrogen Receptor Modulator (SERM) and an agent which exhibits progestogenic activity. The examiner has rejected claims 21-33 as obvious over the prior art. Claims 34-43 are also pending, but have been withdrawn from consideration. We have jurisdiction under 35 U.S.C. § 134. We find that the examiner has not established a prima facie case of unpatentability, and reverse the rejection.

Background

"[T]he most prevalent form of oral contraception . . . combines both estrogen and a progestin." Specification, page 1. "Another well-known use [of estrogen] is long term estrogen replacement therapy . . . for post-menopausal and other estrogen deficient women." Id. "Despite their value, estrogen treatments are also associated with undesirable side effects." Id. One approach to avoiding the ill effects of estrogen therapy is to use a selective estrogen receptor modulator in place of estrogen. Id., page 2.

Selective estrogen receptor modulators (SERMs) - also known as anti-estrogens or selective estrogens - bind estrogen receptors and competitively block the binding of endogenous estrogens. Id., page 4. "However, all such [SERMs] can be, in fact, active estrogens depending on the tissue, dose/regimen and hormonal milieu of the drug exposure." Id., page 2. That is, they can exhibit complex "mixed function agonistic/antagonistic activities" and "[t]he degree to which the [SERM] acts as an estrogen also depends on the particular material and the tissue site." Id. Among the best known of these SERMs are clomiphene, tamoxifen and benzothiophenes like raloxifene. Id., pages 2 and 6. Nevertheless, "[SERM] therapy . . . is not without its own problems." Id., page 2.

> As is know[n], there is a hypothalamic-pituitary-gonadal axis involved in endogenous hormone production. As estrogen binds to its receptors, there is a feedback mechanism which regulates the endogenous production of pituitary gonadotropins and, in turn, estrogen so that the hormonal milieu remains within the physiological range. When [a SERM] binds to the estrogen receptors, altered estrogen feedback mechanisms are implicated in a pharmacological manner compared to when estrogen binds normally. The [SERMs] themselves can induce multiple follicular growth which, in turn, causes the production of endogenous ovarian estrogens. A favorable example is the use of clomiphene for ovulation induction. For the first [SERM] dose administration and continuing for some period of time, the

> endogenous estrogen produced as a consequence of the multiple follicular growth may not appear to pose a problem. However, at some point, which is totally unpredictable and which varies from individual to individual, endogenous estrogen can be produced such that the quantity of estrogen present can elevate blood levels [dramatically] . . . Therefore, while the use of [a SERM] seeks to reduce or modify or eliminate the side effects of estrogen, its use over time may have the reverse effect by inducing an excess concentration of estrogen. Not only may the use of the [SERM] exaggerate the estrogen side effects which it seeks to avoid, but the [SERM] may even eliminate the primary benefit of the administration in the first instance. For example, a "run away" endogenous estrogen can induce ovulation in those situations where the administration of the [SERM] was designed to provide contraception. This feature of anti-estrogen therapy makes the establishment and maintenance of appropriate dosages of anti-estrogen difficult . . . especially when the therapeutic goal is simultaneous[ly] to limit excessive estrogenic impact in one tissue, while [ ] providing adequate estrogenic stimulation in another tissue.

Id., pages 2-3.

"[T]he object of the present invention [is] to keep the hypothalamus and pituitary from becoming deranged [during SERM contraceptive therapy] and thereby prevent multiple follicular growth and the . . . sustained, supraphysiological [endogenous estrogen] elevations which result from ovarian hyperstimulation." Id., pages 3-4. "More particularly, the invention involves superposing upon the use of a selective estrogen receptor modulator, the co-administration of a [ ] progestationally active [compound] . . . [which] may also exhibit androgenic activity" (id., page 4).

The "progestationally active" or "progestogenic" compound may be "progesterone, a synthetic progestin analog or even an anti-progestin having agonistic activity" (id.). Compounds which exhibit both androgenic and progestogenic activity simultaneously include danazol and levonorgestrel. Id., page 8.

"The amount of progestationally and optional androgenically active compound which is administered is that which is effective to regulate endogenous estrogen

secretions to a desired level. Thereby, ovulation can be blocked and endometrial growth and menstruation can be controlled." Id., page 9.

The Claims

Claim 21, the only independent claim on appeal, represents the claimed invention in its broadest aspect:

21. In a method of achieving contraception in a premenopausal human female by administering to the female a contraception effective amount of a contraceptive agent, the improvement which comprises said agent being a combination of a contraception effective amount of a Selective Estrogen Receptor Modulator and an agent which exhibits progestogenic activity, wherein the amount of the agent which exhibits progestogenic activity is effective to ameliorate or eliminate the bleeding side effects of the Selective Estrogen Receptor Modulator.

Thus, the claims require administration of a SERM to a premenopausal human female in an amount effective to achieve contraception, together with a progestogenic agent in an amount effective to ameliorate or eliminate bleeding caused by the SERM.

Discussion

The examiner rejected claims 21-33 under 35 U.S.C. § 103 as unpatentable in view of Jones,[1] Basu,[2] Schane[3] and the Merck Manual.[4] Jones describes benzothiophenes as "useful as orally active anti-fertility agents in birds and mammals . . . [f]or example, . . . undesirable rodents and other small animals including Canidae such as coyotes, foxes, wolves, jackals, and wild dogs, and birds, such as starlings, galls, redwing blackbirds, pigeons, and the like" (Jones, column 9, lines 29-30 and 34-40).

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[1] Jones et al., US Patent No. 4,133,814, issued January 9, 1979
[2] J. Basu, "Antifertility Effect of Three New Clomiphene Analogues on Animals," Japan. J. exp. Med., Vol. 43, pp. 9-15 (1973)
[3] Schane et al., "Fertility in the Rhesus Monkey Following Long-Term Inhibition of Ovarian Function with Danazol," Fertility and Sterility, Vol. 29, No. 6, pp. 692-694 (1978)
[4] The Merck Manual of Medicinal Information, Home Edition, Berkow et al., Eds., Pocket Books, New York, NY, p. 1225 (1997)

Basu describes the varied anti-fertility effects of clomiphene and clomiphene analogs in mice, rats and rabbits. Basu, page 9. Schane reports that danazol is "an oral contraceptive in women when administered continuously." Schane, page 692. Finally, the Merck Manual teaches that "bleeding at irregular times during the menstrual cycle is [a] common" side effect of oral contraceptives containing estrogen and progestin. Merck Manual, page 1225.

According to the examiner, benzothiophenes, clomiphene and danazol are "taught as useful for independently providing contraception, [and] viewed by the skilled artisan as differing from the claimed use, not at all." Final Rejection, July 1, 2004, page 8. The examiner acknowledges that the references do not describe "the concomitant employment of these medicaments" (id.). Nevertheless, the examiner argues that "[i]t is generally considered prima facie obvious to combine compounds each of which is taught to be useful for the same purpose, in order to form a composition which is to be used for the very same purpose . . . combining them flows logically from their having been used individually in the prior art" (Examiner's Answer, page 9, citing In re Kerkhoven, 626 F.2d 848, 205 USPQ 1069 (CCPA 1980)).

With respect to the requirement for an amount of progestogenic compound effective to ameliorate or eliminate bleeding caused by the SERM, the examiner relies on the Merck Manual as teaching that "oral contraceptives are known to cause bleeding," and concludes that "it would have further been obvious to optimize the dosages of the SERMs and progestins in order to effectuate the minimal amount of bleeding possible." Examiner's Answer, page 5.

As explained in In re Kotzab, 217 F.3d 1365, 1369-70, 55 USPQ2d 1313, 1316 (Fed. Cir. 2000) (citations omitted):

> Most if not all inventions arise from a combination of old elements . . . However, identification in the prior art of each individual part claimed is insufficient to defeat patentability of the whole claimed invention. Rather, to establish obviousness based on a combination of the elements disclosed in the prior art, there must be some motivation, suggestion or teaching of the desirability of making the specific combination that was made by the applicant.

It may be fair to say that that "[i]t is generally considered prima facie obvious to combine compounds . . . taught to be useful for the same purpose, . . . to form a composition which is to be used for the same purpose" (Examiner's Answer, page 9), and that the requisite motivation or suggestion flows from the compounds having been used individually for the same purpose. But the situation here is not so simple. The specification teaches that SERMs exhibit estrogen-like effects in some tissues, and anti-estrogen effects in others, depending on the particular SERM, the dose, regimen and hormonal environment. Specification, page 2.

In addition, as appellant points out, Jones (benzothiophenes) and Basu (clomiphenes) "do not deal with human beings" (Reply Brief, page 2), and Greenblatt[5] "indicates one cannot analogize between rats and women" (id.). In particular, Greenblatt teaches that MRL/41, a clomiphene similar to the clomiphene analogs described in Basu, has "pituitary gonadotropin-inhibiting and antifecundity properties" in rats, but "was found to possess a surprising potential for the induction of ovulatory-type cycles in amenorrheic women . . . [as did] a related compound, MER-25" (Greenblatt, page 101, column 1).

[5] Greenblatt et al., "Induction of Ovulation with MRL/41," The Journal of the American Medical Association, Vol. 178, No. 2 (October 14, 1961) (cited by applicant, and considered by the examiner)

The examiner dismisses the Greenblatt reference largely because it "pre-dates the cited references by at least a decade . . . [thus], the skilled artisan would not understand Greenblatt to be a more contemporary teaching regarding SERMS than Jones and Basu" (Examiner's Answer, page 4). However, we agree with appellant that the relative publication dates of the references are beside the point – they are not inconsistent with each other. Their teachings complement each other, and support appellant's assertion that "it is not appropriate to apply teachings cross-species" in this particular area (Reply Brief, page 2).

With respect to the claims' requirement for an amount of progestogenic compound "effective to ameliorate or eliminate the bleeding side effects of the [SERM]" (e.g., claim 21), we note the examiner's reliance on the Merck Manual, but we do not agree that it adds anything to the examiner's rejection. Examiner's Answer, page 5. The Merck Manual simply teaches that bleeding is a common side effect of oral contraceptives containing estrogens and progestins, and the examiner has not begun to explain how this teaching would have led one skilled in the art to combine SERMs and progestins to ameliorate bleeding due to SERMs.

"[T]he examiner bears the initial burden of presenting a prima facie case of obviousness. Only if that burden is met, does the burden of coming forward with evidence or argument shift to the applicant." In re Rijckaert, 9 F.3d 1531, 1532, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993). "It is impermissible to use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is rendered obvious." In re Fritch, 972 F.2d 1260, 1266, 23 USPQ2d 1780, 1784 (Fed. Cir. 1992) (citation omitted). The

examiner may establish a case of prima facie obviousness based on a combination of references "only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references." Id. at 1265, 23 USPQ2d at 1783. On this record, the examiner has not done so.

Accordingly, the rejection of claims 21-33 as unpatentable under 35 U.S.C. § 103 is reversed.

REVERSED

Toni R. Scheiner)
Administrative Patent Judge)
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